Remarks

Claims 1-27 were pending in the subject application. By this Amendment, claim 1 has been amended, claims 21-27 have been cancelled, and new claims 28-34 have been added. Support for the new claims and amendments can be found throughout the subject specification, including for example, at page 9, lines 6-18; page 20, line 31 through to page 21, line 14; page 23, lines 12-16; and page 35, lines 11-19, and in the claims as originally filed. Applicants respectfully assert that new claims 28-34, directed to mammalian tissue comprising a genetically modified cell of the invention, are encompassed within the elected invention. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-20 and 28-34 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Applicants' note that the Examiner indicates that claim 20 is withdrawn from consideration on the grounds of being drawn to non-elected subject matter. Claim 20 is directed to species of the elected invention, and not to a non-elected invention. Thus, Applicants respectfully assert that the claim is encompassed within the elected invention. Moreover, 37 CFR §1.141(a) specifically provides that "...more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application,..." Accordingly, reconsideration and rejoinder of claim 20 in the subject application is respectfully requested.

Claim 17 is rejected under 35 USC §112, second paragraph, as indefinite. The Examiner asserts that the term "endogenous" in claim 17 is unclear as to its meaning in view of the recitation of an "exogenous polynucleotide" in claim 1. Applicants respectfully assert that the term "endogenous" in claim 17 is clear. Applicants respectfully assert that a person of ordinary skill in the art would understand that use of the term "endogenous" means that the polypeptide of the claim is the same as one that is usually produced or capable of being produced by the cell in the absence of genetic modification with the claimed polynucleotides. Thus, a polynucleotide can be exogenous to a cell and yet can encode a polypeptide that is endogenous to the cell. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 1-9, 11, and 14-19 are rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Juan *et al.* (2001). Claim 10 is rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Juan *et al.* (2001), and further in view of Nicklin *et al.* (2002). Claims 12 and 13 are rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Juan *et al.* (2001), and further in view of Turgeman *et al.* (2001). Tang *et al.*, the primary reference in all of these rejections, is cited as teaching that coronary artery disease frequently involves repcated bouts of myocardial ischemia, and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a "vigilant vector" gene therapy system was developed and tested in a rat embryonic cardiac myoblast. Tang *et al.* is also cited as teaching that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Tang *et al.* is also cited as teaching that the promoter and reporter gene are separated into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). The Juan *et al.* reference is cited as teaching (i) adenovirus-mediated gene transfer of HO-l in arteries reduces iron overload and inhibits lesion formation in apolipoprotein E (apoE)-deficient mice, and (ii) heme oxygenase (HO) is a rate-limiting enzyme in heme catabolism and one of the isozymes, HO-1, is a stress-response protein and can be induced by a variety of oxidation-inducing agents, and that induction of HO-l leads to the degradation of pro-oxidant heme to carbon monoxide (CO) and biliverdin. The Nicklin *et al.* reference is cited as teaching the use of adeno-associated virus (AAV)-based vectors. The Turgeman *et al.* reference is cited as teaching human mesenchymal stem cells are pluripotent and are useful for skeletal gene therapy and can be genetically engineered to express desired therapeutic proteins. The Examiner concludes that it would have been obvious to an ordinarily skilled artisan to combine the teachings of the cited references to arrive at Applicants' claimed invention. Applicants respectfully traverse these grounds of rejection.

Applicants respectfully assert that the cited references, taken alone or in combination, do not teach or suggest the claimed invention. Tang *et al.* is the primary reference cited under each of the 35 USC §103 rejections. By this Amendment, Applicants have amended claim 1 to recite that the cell is a stem cell or a progenitor cell. The Tang *et al.* reference does not teach or suggest the use of stem or progenitor cells, and more particularly, does not teach or suggest the use of cells autologous

to the tissue. Moreover, the vector described in the Tang *et al.* reference was designed specifically for injection directly into heart tissue and not for use in stem cells.

Applicants respectfully assert that the combination of a gene switch/biosensor and a gene amplification system in a stem cell or a progenitor cell is novel and not obvious over the teachings of the cited references. Applicants' claimed invention advantageously provides for cell therapy wherein a patient can have their own stem or progenitor cells prepared from their own tissue (*e.g.*, bone marrow) and then the cells can be provided with a vector (*e.g.*, hypoxia gene switch/transgene) outside the body before injecting the modified cells directly into the target tissue (*e.g.*, heart) of the patient. The claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). It was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention. When bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days. The present invention solved the problem of poor cell survival that occurs in stem cell therapy. The Tang *et al.* reference does not teach or suggest anything of relevance in regard to the problem of implanted stem cell survival.

The Tang *et al.* reference describes testing different types of gene switches, including single vector and double vector models. The rat myoblast cell line H9c2 referred to in the Tang *et al.* reference was only used for testing the vector. It was not used for stem cell transplantation. Nowhere in the Tang *et al.* reference did the authors teach or suggest an approach for improving stem cell survival in therapy. The work reported in the Tang *et al.* reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene switch.

Moreover, Applicants respectfully assert that the cited references do not teach or suggest a mammalian tissue comprising a genetically modified mammalian stem or progenitor cell as claimed in new claims 28-34. There is no teaching or suggestion in any of the cited references to provide mammalian tissue with a genetically modified stem cell or progenitor cell of the invention. As noted above, the Tang *et al.* reference is concerned with direct gene therapy and not with cell therapy.

Thus, Tang *et al.* is only relevant with regard to transforming cells within a tissue with a nucleic acid vector.

The secondary references, Juan *et al.*, Nicklin *et al.*, and Turgeman *et al.*, cited under the §103 rejections fail to cure or overcome the deficiencies of Tang *et al.*, the primary reference. The Juan *et al.* reference is irrelevant as it does not teach or suggest that heme oxygenase 1 is cell protective against apoptosis.

As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicants' claimed invention in the cited references. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

DRP/trt/mv